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Norriss Hetherington

MEDAWAR, PETER BRIAN (*b.* Rio de Janeiro, 28 February 1915, *d.* London, 2 October 1987), *immunology, transplant biology, medicine.*

Sir Peter Medawar is best remembered for developing the theory of acquired immunological tolerance, thus laying the foundation for successful organ and tissue

transplantation. For this work he received, along with Sir Frank Macfarlane Burnet, the Nobel Prize for Physiology or Medicine in 1960. A central figure in twentieth-century British science, as a gifted writer he also explored the beauty and power of scientific thinking for a wider public.

Early Years. Medawar was born the son of Nicholas Agnatius Medawar (a salesman of Lebanese extraction) and Edith Muriel Dowling, who was British. He spent his early years in Brazil, where he learned Portuguese and developed a love of opera. The family returned to England for a brief period, and Medawar and his brother remained in England when his parents returned to Brazil. From 1928 to 1932 he attended Marlborough College, where he endured harassment due to his lack of athletic ability and his Middle Eastern features, which led others to assume he was Jewish. It was, however, at Marlborough that he developed a love of biology, a passion that he took to Oxford, where he studied zoology at Magdalen under the tutelage of the eminent anatomist John Z. Young. He received a first in zoology in 1935, and in the same year was appointed Christopher Welch Scholar and Senior Demonstrator at Magdalen. At this time, he began working at the Sir William Dunn School of Pathology under the future Nobel laureate Sir Howard Florey; he would remain in Oxford until after World War II. During this period of his life, he would be Rolleston Prizeman (1942), Senior Research Fellow of St. John's College (1944), and university demonstrator in zoology and comparative anatomy (also 1944). In 1946 he was elected a Fellow of Magdalen; he was awarded a DSc in 1947, and soon afterward was appointed Mason Professor of Zoology at the University of Birmingham (at the suggestion of Sir Solly Zuckerman).

On Growth and Form. Medawar's first scientific work involved studying extracts from malt that inhibited the growth of chick fibroblasts (connective tissue cells), studies that versed him in the emerging field of tissue culture. The factor identified was a carbohydrate rather than a protein and has not as of 2007 been fully characterized. When he showed Florey the first draft of his manuscript, Florey was not impressed, saying the paper was more philosophical than scientific; yet the paper, "A Factor Inhibiting the Growth of Mesenchyme," was published in 1937 following Florey's recommendation that Medawar consult with some chemists. As Mitchison comments, this paper already had many of the distinctive features of Medawar's later work: "powerful ideas, able to place a simple fact in the widest possible context; a highly distinctive style, able to manipulate with total confidence a vocabulary far wider that that usually employed within science; and the authority … to assign previous work to its place within a novel conceptual framework" (1990, p. 286).

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This work spurred Medawar on to examine the growth of cells in culture. Building on the works of Charles Sedgwick Minot, Ludwig von Bertalanffy, and Julian Huxley, and using mathematical modeling of growth, Medawar assimilated and clarified the earlier works while investigating aspects of it in depth. While Medawar would shift his research during World War II into the field that would bring him eventual fame, he often returned to the problems of growth in all its manifestations and, for example, extensively discussed human demographics in his 1959 Reith Lectures for the British Broadcasting Corporation (BBC). In addition, he examined D'Arcy Wentworth Thompson's analyses of relative growth and applied them to human problems, and he was one of the few who attempted to utilize—albeit unsuccessfully—Thompson's method of transformed coordinates, a method that would only be mathematically formalized in the 1980s with the development of geometric morphometrics.

The Immunology of Transplantation. Medawar's work during World War II would eventually create a new branch of science, the immunology of transplantation. With the war raging—and bombings increasing the number of burn victims—the problem of skin graft rejection became particularly serious. Conventional wisdom held that preventing rejection was a matter of surgical skill; Medawar's work would demonstrate that this was instead a biological problem.

The War Wounds Committee of the British Medical Council assigned Medawar to work with Thomas Gibson at the Burn Unit at Glasgow Infirmary. In 1943 they produced a paper ("The Fate of Skin Homografts in Man") that would for the first time use experimentation and observation to systematically study the rejection process. To do so, Gibson transplanted a set of grafts (termed *autografts*) taken from a burn victim and a second individual (termed *homografts*, or later *allografts*) onto the patient's back. At intervals, some of these small "pinch" grafts were removed and studied histologically by Medawar, who observed that the autografts succeeded, but allografts failed after initial acceptance. Importantly, a second set of allografts were rejected more rapidly than the first. Thus, to Gibson and Medawar, the rejection process appeared to have characteristics of an immunological response.

Medawar returned to Oxford and continued his study of allograft rejection using rabbits as his model organism. In a series of papers for the War Wounds Committee, he confirmed the existence of the time delay before rejection commenced, used demographic techniques to study survival times for grafts, and described invasion of the grafts by lymphocytes, thus strengthening the case for rejection being due to an immune reaction.

Central to their work was the examination of skin transplantation in twin cattle. The Edinburgh geneticist Hugh P. Donald had challenged Medawar to find a method to distinguish between dizygotic and monozygotic twins in cattle. Medawar suggested that skin grafting would provide such a test, reasoning that if grafts were mutually accepted, the twins would have to be monozygotic (genetically identical). Much to the surprise of Medawar and Billingham—who were working with two technicians on an Agricultural Research Council farm in Staffordshire—virtually all the grafts were accepted, including those from twins that were definitely dizygotic. What could have caused such tolerance? As it happens, in 1945 an American, Raymond D. Owen, had shown that dizygotic twin cattle have two populations of red blood cells: their own and cells derived from their twin while in the womb (in this, cattle are different from humans due to their synchorial placenta). Medawar and Billingham realized that the acceptance of foreign grafts was due to this exchange, thus supporting a hypothesis put forward in 1949 by Burnet and Frank J. Fenner. Billingham, Medawar, and Brent then set out to experimentally examine this acquired tolerance using inbred strains of mice.

Within two years, the team had successfully induced tolerance to skin allografts by introducing donor cells into fetal mice. Cells were prepared from the spleen, testes, and kidney of a donor and placed in the abdominal cavity of a fetal recipient. This resulted in tolerance of the recipient for allografts from individuals who were genetically identical to the donor. The results were described in a paper published in *Nature*—a paper that, fifty years later, the British Transplantation Society described as the most important paper in the history of transplantation. Its importance lay in demonstrating that graft rejection could be overcome by purely biological means that did not require immunosuppressive drugs. A series of papers ("Quantitative Studies on Tissue Transplantation Immunity") followed in rapid succession, and the third paper was seen by Brent as their magnum opus (and by Mitchison as the group's "crowning glory"). Appearing in *Philosophical Transactions of the Royal Society* in 1956, the paper described a series of experiments which established that tolerant individuals were usually chimeric (i.e., possessing a combination of donor and recipient cells), examined possible mechanisms of tolerance, and concluded that tolerance was brought about by a deletional mechanism. (It was Burnet who would famously propose elimination of self-reactive lymphocyte clones in 1960.) While the mechanism was unknown in 1956, what was clear was that tolerance-of-self (the immune system's ability to tolerate the organism's own cells) must itself be acquired by exposure of the system to self-molecules during the process of development.

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The Nobel Prize. In 1960 Medawar and Burnet were awarded the Nobel Prize for their work on immunological tolerance. Introducing the laureates, Sven Gard of the Royal Caroline Institute noted that "[i]mmunity is our perhaps most important defense against a hostile surrounding world. By penetrating analysis of existing data and brilliant deduction, and by painstaking experimental research you have unveiled a fundamental law governing the development and maintenance of this vital mechanism." While Burnet and Fenner had speculated about the existence of tolerance in 1949, it took the experimental work of Medawar, Billingham, and Brent to demonstrate the phenomenon. It may be wondered why Billingham and Brent were not included in the award. As Brent himself notes, that would have meant that Fenner and, indeed, Owen would probably have had to be included as well. Medawar himself publicly acknowledged the contributions of Billingham and Brent on British television the day the award was announced and in his memoirs stated that "I was terribly sorry that the distinction could not be so far divided as to have included my friends Bill [Billington] and Leslie. I could—and did—share my portion of the prize money with them, but that's not the same thing."

Later Work. Moving from UCL in 1962, Medawar was appointed director of the National Institute for Medical Research and, in 1971, head of the transplantation section of the Medical Research Council's Clinical Research Center, a post he held until the year before his death. The Nobel Prize brought fame to Medawar and, while he became a public intellectual, he continued to investigate aspects of immunology. He studied immunological privileged sites (places such as the brain where lymphocytes do not occur and thus where allografts can survive indefinitely). In particular, he examined why the mammalian fetus is not rejected, deciding that neither privilege nor the action of hormones can explain acceptance of the foreign tissue. With Sparrow, he continued his examination of the use of corticosteroids to prolong skin grafts. He examined the use of antilymphocyte serum as an agent to prevent graft rejection. He continued this scientific research even after his stroke of 1969, while spending a significant amount of time communicating his views on scientific method to fellow scientists and the public. (A representative sample of these writings is collected in *Pluto's Republic* and *The Threat and the Glory*.)

Influenced by T. D. "Harry" Weldon, A. J. Ayer, and Karl Popper, Medawar was particularly interested in seeing science as a hypothetico-deductive enterprise that was not restricted to the examination of scientific problems. While experiment and testing were important, Medawar saw the true mark of science, which he famously described as the "art of the soluble," to be the creative act in which

a new idea was generated. Following from Popper, he held that these ideas could never be formally proven true.

Medawar's view on biology is best exemplified by a portion of his Nobel banquet speech given on 10 December 1960:

> It is [...] a sign of the times—though our brothers of physics and chemistry may smile to hear me say so—that biology is now a science in which theories can be devised: theories which lead to predictions and predictions which sometimes turn out to be correct. These facts confirm me in a belief I hold most passionately—that biology is the heir of all the sciences.

Medawar's interest in the theory of biology and the nature of scientific inquiry is nicely illustrated in his 1974 paper presenting "A Geometric Model of Reduction and Emergence." In this short piece, he noted that biology contains "contextually distinctive notions" at the level of the organism that are "peculiar to and distinctive of" that level and are thus "not obviously reducible to the notions of the level immediately above [ecology] or higher still [chemistry and physics]" (p. 57). These notions include "heredity," "infection," "immunity," "sexuality," and "fear." He goes on to provide a thought-provoking discussion of "the sense of diminishment" that results from "analytical reduction" (p. 62). Yet this antireductionism did not lead to "fuzzy" thinking—one has only to read his justly famous review of Pierre Teilhard de Chardin's *The Phenomenon of Man* to see that was not the case.

In addition to his Nobel Prize, Medawar received much recognition for his work. He was elected Fellow of the Royal Society of London (1949), was the Society's Croonian Lecturer in 1958, and received its Royal Medal in 1959. He was awarded a C.B.E. (Commander of the British Empire) in 1958, a knighthood in 1965, a C.H. (Companion of Honour) in 1972, and an O.M. (Order of Merit) in 1981.

In February 1937 Medawar married Jean Shinglewood Taylor (1913–2005), whom he met as an undergraduate in Oxford, and with whom he had four children. In 1969 Medawar suffered a stroke while giving an address at the British Association for the Advancement of Science's annual meeting in Exeter. This left him partially paralyzed and under the care of Jean, who collaborated with him on some of his later writings. He suffered several more strokes and eventually died from one in 1987. Further details of his life can be found in his autobiographical *Memoir of a Thinking Radish* (1986) and Jean's memoir, *A Very Decided Preference* (1990).

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John M. Lynch

MEEHL, PAUL EVERETT

(*b.* Minneapolis, Minnesota, 3 January 1920; *d.* Minneapolis, 14 February 2003), *psychology, philosophy, psychiatry.*

Meehl was a theoretical psychologist and philosopher of science who contributed several important conceptual formulations to psychology, most notably a demonstration of the superiority of actuarial against intuitive prediction. A practicing psychotherapist, he played an important role in the medicalizing of American psychology.

Polyvalent Beginnings. Meehl came to psychology out of deep personal motives: His father's suicide during the Great Depression and his mother's death five years later from a misdiagnosed brain tumor led him to question fatal human motives and fallible judgment. Intellectually precocious and voracious, his first encounter with his future work was his reading, at age twelve, Karl Menninger's *The Human Mind*. In his autobiography, Meehl said he found this blend of contemporary psychiatric nosology and therapeutic optimism a "healing Damascus experience" (1989, p. 339). Before Meehl was fifteen he had read extensively in psychology—popular behaviorisms as well as Sigmund Freud—and revealed a taste and talent for epistemology, reading Bertrand Russell. He was especially influenced by Alburey Castell's lucid 1935 textbook *A College Logic*, and honed his formal logical skills debating with adolescent peers. Castell, a University of Minnesota faculty member, was limned as Frazier's critical interlocutor in B. F. Skinner's *Walden Two;* similarly, Meehl became a gadfly critic of psychology's scientific enterprise.

Meehl entered the University of Minnesota in 1938, intending to follow the premedical course, but he migrated to psychology, graduating with an undergraduate degree (with a minor in biometry) in 1941. His main undergraduate influence in psychology was Donald G. Paterson, a practical psychometric specialist and an early proponent of vocational guidance, from whom he gained expertise in the measurement of human abilities and a predisposition to consider psychology as inseparable from its applications. It was fortunate that, in 1940, Herbert Feigl moved from Iowa to Minnesota, where he finished the rest of his career. Feigl, a highly cultured colleague of the Viennese logical positivists, found in Meehl a kindred spirit and a lifelong friend. Through Feigl, Meehl had access to a rich, well-articulated theoretical approach to the unity of science and liberalized versions of neopositivism. Meehl remained at Minnesota for graduate work—indeed, he remained at Minnesota for the remainder of his career, retiring as Regents' Professor of Psychology in 1990—and was mentored by another exponent of the style of Minnesota psychology known as "Dustbowl Empiricism," Starke Rosecrans Hathaway. Hathaway was one of the earliest medical clinical psychologists in the United States and had just finished assembling, in conjunction with the neuropsychiatrist J. Charnley McKinley of the medical faculty, a psychometric instrument designed specifically for identifying and classifying psychiatric disorders, the Minnesota Multiphasic Personality Inventory, or MMPI.

Meehl, rated unfit for service during World War II because of a heart defect, remained at Minnesota during the war years. While continuing to work with Feigl and Hathaway, Meehl became one of the group of graduate students who associated closely with Skinner in the midst of a most fertile conceptual period, when he was working simultaneously on shaping, language, and the social implications of behaviorism, leading to the writing of *Walden Two*. Skinner, after moving to Indiana from Minnesota at the end of the war, thought highly enough of Meehl that he offered him his first academic position. Meehl, however, declined it, having established himself as not only a psychometric specialist but also as a clinician, seeing his first clients in 1942. Meehl received a PhD in clinical psychology in 1945, entering that profession just as it came of age in economic and social terms. His thesis focused on people with psychopathology who are able to compensate for it and appear normal. The search for latency, psychopathic and otherwise, determined the direction of his career.

The Search for Latent Entities. From the outset, Meehl strove to create a theoretical framework that could contain both clinical and experimental psychology and that would allow the existence of latent mental entities. Meehl was impressed early on by an experience in which Hathaway gave him several psychiatric case studies and asked him, blind to the diagnosis and to the MMPI profile, to find